

EXTENDED REPORT

Prediction of radiological outcome in early rheumatoid arthritis in clinical practice: role of antibodies to citrullinated peptides (anti-CCP)

K Forslind, M Ahlmén, K Eberhardt, I Hafström, B Svensson, for the BARFOT study group

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See end of article for authors' affiliations

Correspondence to:
Dr B Svensson,
Blistorpsvägen 105, 290
38 Villands Vånga,
Sweden; bjoern.
svensson@swipnet.se

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Objective: To investigate the role of anti-cyclic citrullinated peptide antibody (anti-CCP) for the prediction of radiological outcome in patients with early rheumatoid arthritis.

Methods: Anti-CCP was assessed at baseline in 379 patients with early rheumatoid arthritis (disease duration <1 year). Radiological joint damage and progression were assessed by Larsen score after two years of follow up (end point) and used as outcome variables. The prognostic value of anti-CCP and other demographic and disease related baseline variables were assessed by univariate and multivariate analyses, including calculation of odds ratios (OR), predictive values, and multiple logistic regression models.

Results: The presence of anti-CCP was associated with significantly higher Larsen score both at baseline and at end point. Univariate predictor analysis showed that anti-CCP had the highest significant OR for radiological joint damage and progression after baseline Larsen score, followed by rheumatoid factor, erythrocyte sedimentation rate (ESR), C reactive protein, age, smoking status, and sex. In stepwise multiple regression analyses, baseline Larsen score, anti-CCP, and ESR were selected as significant independent predictors of the radiological outcomes.

Conclusions: There is good evidence for an association of anti-CCP with radiological joint changes in rheumatoid arthritis. Anti-CCP is an independent predictor of radiological damage and progression. Though prediction in early rheumatoid arthritis is still far from perfect, the use of anti-CCP in clinical practice should make it easier for rheumatologists to reach judicious treatment decisions.

Rheumatoid arthritis is an inflammatory disease of unknown cause. The inflammation of joints and surrounding tissues and sometimes of extra-articular structures may cause severe disability and increased mortality. The course of rheumatoid arthritis is varied, ranging from mild to aggressive forms, the latter being very difficult to cope with. It has been shown that early diagnosis and treatment reduce joint destruction, preserve function, and improve survival.¹ However, prognostic factors capable of guiding the rheumatologist to optimal treatment in the individual patient are largely lacking in clinical practice.

Risk factors have been identified in groups of patients with different outcomes such as joint destruction and disability. Baseline radiographic joint changes, presence of rheumatoid factor (RF), specific HLA-DRB1 genotypes, high disease activity, high disability scores, and high levels of acute phase proteins are examples of such factors (for reviews, see Harrison and Symmons² and Scott³).

Binding of antiperinuclear factor (APF) and antikeratin antibody (AKA) to filaggrin in buccal and oesophageal mucosal cells, respectively, has a high specificity for the diagnosis of rheumatoid arthritis.⁴ These antifilaggrin antibodies may also be markers of a more severe disease course.⁵ It has been shown recently that APF and AKA bind to peptides containing the modified amino acid citrulline and that antibodies to synthetic cyclic citrullinated peptides (anti-CCP)⁶ are even more specific for rheumatoid arthritis,⁷ and may also have prognostic capacity.⁸ Furthermore, anti-CCP have been incorporated into newly proposed diagnostic criteria for rheumatoid arthritis and proved to be strongly associated with erosive arthritis.⁹ However, further studies on larger patient populations are needed to assess the value of anti-CCP in clinical practice.

In the present study on patients with early rheumatoid arthritis participating in a long term observational study of this disease, we investigated the role of anti-CCP in predicting radiological outcome.

Patients

The patients in the study are taking part in the "BARFOT" (better anti-rheumatic pharmacotherapy) study,¹⁰ a Swedish multicentre observational study of patients with recent onset rheumatoid arthritis (disease duration one year or less), satisfying the 1987 American College of Rheumatology classification criteria.¹¹

During the period from July 1993 to June 1997, 453 white patients were consecutively included in the BARFOT study. Sera for analysis of antibodies to cyclic citrullinated peptides (anti-CCP) were available in 379 of these patients and missing in 74. These 379 patients constitute the study population. The 74 patients lacking sera for analysis of anti-CCP had similar demographic and baseline clinical characteristics to the study population except for significantly lower disease activity score (DAS28; see below) ($p = 0.003$) and a lower proportion of RF positivity ($p = 0.018$).

All patients gave their informed consent and the ethics committees approved the study.

Abbreviations: AKA, antikeratin antibody; AFA, antifilaggrin antibody; APF, antiperinuclear factor; BARFOT, better anti-rheumatic pharmacotherapy study; CCP, cyclic citrullinated peptides; DAS, disease activity score; DMARD, disease modifying antirheumatic drug; HAQ, health assessment questionnaire; ICC, intraclass correlation coefficient; NPV, negative predictive value; PPV, positive predictive value; RF, rheumatoid factor; VAS, visual analogue scale

METHODS

Antibodies to cyclic citrullinated peptide (anti-CCP)

Serum antibodies directed to cyclic citrullinated peptide were analysed using the Immunoscan-RA enzyme linked immunosorbent assay (ELISA) CCP2 test (Euro-Diagnostica, Malmö, Sweden), carried out according to the manufacturer's instructions. Samples yielding values above the standard curve were further diluted to obtain definite values for all subjects investigated. A titre above 25 units/ml was regarded as positive. Using this cut off point the specificity was 97% for material from 99 healthy individuals.

Rheumatoid factor

Rheumatoid factor was analysed using the Serodia rheumatoid arthritis agglutination test (Fujirebio Inc, Tokyo, Japan) according to the manufacturer's instructions. The assay was calibrated to WHO RF reference serum 64/002 immediately before batch analysis of the samples. Five per cent of 100 healthy blood donors were weakly RF positive at a dilution corresponding to 20 IU/ml, and this level was therefore chosen as the cut off value. A titre of 20 IU/ml was regarded as positive.

The analyses of RF and anti-CCP were carried out in the department of clinical immunology, Uppsala University Hospital, Uppsala, Sweden.

Rheumatoid arthritis associated alleles

HLA-DRB104 genotyping was undertaken as described earlier.¹² The genotyping was done at the Regional Blood Centre, Sahlgrenska University Hospital, Göteborg, Sweden.

Disease activity and disability

Disease activity was assessed by the disease activity score, using a 28 joint score (DAS28).¹³ Acute phase reactions were measured by erythrocyte sedimentation rate (ESR; mm/h) and C reactive protein (mg/l) using standard laboratory methods. Global health and pain were assessed by a 0–100 mm horizontal visual analogue scale (VAS). Functional disability was evaluated using the Swedish version of the Stanford health assessment questionnaire (HAQ).¹⁴

Radiographic measurement

Larsen scores were calculated to assess joint destruction. Postero-anterior radiographs were taken of hands, wrists, and forefeet at enrolment and after two years. Radiographic damage was classified by comparison with standard reference films according to the method of Larsen *et al*—that is, the Larsen–Dale index.¹⁵ The joints assessed for this index are the wrists, where the scored numbers are multiplied by 5, all metacarpal-phalangeal joints (= 10), all proximal interphalangeal joints (= 8), both first interphalangeal joints in the hands (= 2), metatarso-phalangeal joints II–V (= 8), and both first interphalangeal joints in the feet (= 2). Thus 32 joints are scored in all. Each joint is graded 0–V, as follows:

- grade 0: no abnormality;
- grade I: slight abnormality with one or more of the following criteria: soft tissue swelling, juxta-articular osteoporosis, slight narrowing of the joint space;
- grade II–V: erosion and narrowing of the joint space of increasing severity as illustrated in the standard reference radiographs referring to the grade of damage of bone and cartilage, respectively.

The degree of erosive damage is the most decisive criterion in grading. The Larsen score is the total sum of the grading in all 32 joints, range 0 to 200.

The radiographs were read in chronological order by one blinded observer (KF). The intraobserver reliability was

assessed by calculating the intraclass correlation coefficient (ICC) from a random sample of 20 pairs of radiographs from baseline and end point. These films were read twice with an interval of two weeks. The ICC for the baseline films was 0.97 (95% confidence interval (CI), 0.93 to 0.99), and for the films taken after two years, 0.99 (0.98 to 0.99).

Statistics

Statistical analyses were done using SPSS 11.5 statistical software (SPSS Inc, Chicago, Illinois, USA). For the ICC, a two way mixed effects model was used. The Mann–Whitney U test was used for between-group comparisons, the Wilcoxon signed rank test for paired variables, and the χ^2 test for differences between proportions.

Odds ratios (OR), sensitivity and specificity, and predictive values of possible predictors for radiological outcomes were calculated. If continuous they were categorised by their median baseline value as cut off.

A forward stepwise logistic regression analysis was carried out to find the best model for predicting radiological outcome. The dependent variables were dichotomised as follows:

Joint damage was defined as present if the end point Larsen score was 10 (median value) or higher, otherwise not present. *Radiological progression* was defined as present if the difference between end point and baseline Larsen score was 8 (median value) or higher, otherwise not present. As the x rays were read by one reader only, radiological progression could not be based on a calculation of the smallest detectable difference (SDD).¹⁶

For the logistic regression analyses, the independent variables were selected according to the univariate analysis ($p < 0.05$).

All significance tests were two tailed and conducted at the 0.05 significance level.

To control for multiple significance, the upper limit of the expected number of false significances was calculated as follows:

$$\text{Upper limit of expected number} = \alpha (N - n(\alpha)) / (1 - \alpha)$$

where N = number of tests; $n(\alpha)$ = number of significances on level α ; and α = significance level.

The upper limit for tables 1 to 3 is equal to 0.26. Thus, of the significances reported in these tables, only 0.26 significance in each table is expected to be false and it is therefore likely that all significances are real. In tables 4 and 5, all p values are by definition significant so for those tables no adjustment is necessary.

RESULTS

Baseline characteristics

Three hundred and sixteen sera were obtained at inclusion and 63 within three months thereafter. Antibodies to citrullinated peptides (anti-CCP) were present in 208 (55%) of the 379 sera. The frequency of anti-CCP positivity was similar in patients with sera obtained at baseline and after three months (54% and 62%, respectively, $p = 0.22$).

The baseline characteristics of the patients are presented in table 1.

The median age of the patients was 55 years, 65% were women, and the median disease duration was six months. Sixty per cent of the patients were current or previous smokers, 61% were RF positive, and 52% (of 185 typed patients) had one or two HLA-DRB1*04 alleles (DRB1*04). In relation to clinical characteristics, the median HAQ score was 0.9, pain VAS 44 mm, C reactive protein 19 mg/l, ESR 29 mm/h, DAS 28 5.10, and Larsen score 4.

Table 1 Baseline characteristics of the 379 patients, 208 with and 171 without antibodies to cyclic citrullinated peptides (anti-CCP)

	Valid values	All patients	Patients with anti-CCP		Difference† (p value)
			Negative	Positive	
Age (years)	379	55 (45 to 67)	55 (41 to 71)	55 (46 to 65)	0.51
Sex (female)	379	247 (65%)	115 (67%)	132 (64%)	0.44
Disease duration (months)	379	6 (4 to 8)	6 (3 to 8)	6 (4 to 9)	0.36
Smoking status (current or previous smoker)	379	226 (60%)	88 (52%)	138 (66%)	0.003
Rheumatoid factor positive	373	229 (61%)	42 (25%)	187 (91%)	0.0005
HLA-DRB1*04 present	185	97 (52%)	34 (38%)	63 (66%)	0.0005
HAQ score (0–3)	363	0.90 (0.50 to 1.38)	0.95 (0.50 to 1.36)	0.90 (0.40 to 1.38)	0.913
Pain VAS (0–100 mm)	366	44 (25 to 66)	40 (25 to 60)	46 (25 to 67)	0.36
C reactive protein (mg/l)	364	19 (6 to 43)	10 (4 to 35)	23 (10 to 52)	0.0005
ESR (mm/h)	378	29 (14 to 50)	22 (9 to 39)	36 (21 to 56)	0.0005
DAS28 (0–10)	371	5.10 (4.22 to 5.85)	4.98 (4.15 to 5.74)	5.30 (4.29 to 6.10)	0.046
Larsen score (0–200)	342	4 (0 to 10)	2 (0 to 10)	5 (0 to 11)	0.008

Values are median (25th to 75th centile) or n (%).

†Upper limit of expected number of false significances = 0.26.

DAS28, 28 joint disease activity score; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; VAS, visual analogue scale.

Smoking, RF positivity, and the presence of DRB1*04 were significantly more common in patients with anti-CCP, and values for C reactive protein, ESR, DAS28, and Larsen score were higher in these patients (table 1).

Clinical course

The patients were not treated with disease modifying antirheumatic drugs (DMARDs) or corticosteroids before inclusion in the study. At baseline 250 of the patients (66%) were given DMARDs, 36% methotrexate, 51% sulphasalazine, 13% some other DMARD, and one was given methotrexate and sulphasalazine in combination. At the end point 254 patients had DMARD treatment (49% methotrexate, 22% sulphasalazine, 19% some other DMARD, 10% combination therapy).

At baseline 167 patients were receiving low dose prednisolone (mean (SD) daily dose, 8.30 (2.45) mg), and at end point 155 patients were on prednisolone (5.90 (2.70) mg/day).

During the two year follow up a highly significant improvement occurred in both groups of patients (with and without anti-CCP) in indices of function and disease activity such as HAQ score ($p = 0.0005$), DAS28 ($p = 0.0005$), ESR ($p = 0.0005$), and C reactive protein ($p = 0.0005$).

Comparing anti-CCP positive with anti-CCP negative patients, at end point the anti-CCP positive patients had higher DAS28 (median 3.44 ν 2.88, $p = 0.0005$), higher C reactive protein (median 10 ν 5, $p = 0.0005$), and a higher ESR (median 18 ν 10, $p = 0.0005$).

Radiology was available in about 90% of patients—342 at baseline and 333 at end point. At baseline, 36% of the patients with x rays available had a Larsen score of zero, and at end point, 21%. The Larsen score increased significantly ($p = 0.0005$) during the observation time (median (25th to 75th centile), 4 (0 to 10) at baseline and 10 (2 to 22) at end point). The median difference (end point to baseline) in Larsen score was 8 (2 to 18). Differences in Larsen score between anti-CCP positive and anti-CCP negative patients are reported below.

Anti-CCP, RF, and DRB1*04

Anti-CCP was positive in sera from 208 of 379 patients (55%), and RF in sera from 235 of 374 patients (63%). Rheumatoid arthritis associated alleles (DRB1*0401, 0404, 0405, and 0408) were present in 97 of 185 tested cases (52%). Twenty one patients had a “double dose” of DRB1*04.

Anti-CCP and RF were closely associated: 50% of the patients were both anti-CCP positive and RF positive, and

34% lacked both antibodies ($\chi^2 = 167.6$, $p = 0.0005$). There was an association between anti-CCP and DRB1*04, in that both tests were positive in 34% and both were negative in 30% ($\chi^2 15.1$, $p = 0.0005$). There was also an association between RF positivity and the presence of DRB1*04 ($\chi^2 = 5.4$, $p = 0.02$).

Larsen scores in patients with and without anti-CCP

Compared with anti-CCP negative patients, the anti-CCP positive patients had significantly higher Larsen scores at baseline (median (25th to 75th centile), 5 (0 to 11) ν 2 (0 to 10), $p = 0.008$) and at end point (15 (5 to 27) ν 5 (0 to 14), $p = 0.0005$); they also had a larger change in Larsen score from baseline to end point (12 (4 to 23) ν 4 (0 to 12), $p = 0.0005$).

Univariate analysis of predictors of radiographic outcome

Odds ratios, sensitivity, specificity, and positive and negative predictive values (PPV, NPV) of anti-CCP, RF, DRB1*04, age, sex, smoking status, disease duration, HAQ score, pain VAS, C reactive protein, ESR, DAS28, and baseline Larsen score for radiological damage and progression were calculated.

As shown in tables 2 and 3, the baseline Larsen score had the highest odds ratios for severe radiological damage and progression (12.9 and 9.9, respectively), next to anti-CCP positivity with odds ratios of 3.6 and 2.9, followed by RF positivity, high ESR, and high C reactive protein. Greater age, smoking, and male sex also predicted radiological damage and progression. The odds ratios for disease duration, DAS28, DRB1*04, pain VAS, and HAQ score were not statistically significant.

As also shown in tables 2 and 3, the Larsen score had the highest sensitivities and predictive values for radiological outcomes. Anti-CCP and RF had somewhat lower values. ESR, C reactive protein, age, and smoking status showed sensitivities and PPVs of around 0.6. The remaining variables had poor predictive values.

The predictive values for radiological damage and progression in patients with positive tests for both anti-CCP and RF were similar to those in patients who were positive for only one of the two tests (data not shown).

Multivariate analysis of independent predictors of radiological outcome

The following baseline variables with a p value of less than 0.05 in the univariate analysis were included in the multiple

Table 2 Univariate analysis of baseline variables as possible predictors of radiographic damage

Variable	OR (95% CI)	p Value†	Sensitivity	Specificity	PPV	NPV
Larsen score ≥ 4	12.9 (7.6 to 22.0)	0.0005	0.79	0.77	0.79	0.78
Anti-CCP present	3.6 (2.3 to 5.7)	0.0005	0.71	0.65	0.65	0.66
RF present	2.7 (1.7 to 4.3)	0.0005	0.73	0.61	0.61	0.63
ESR ≥ 29 mm/h	2.7 (1.7 to 4.2)	0.0005	0.63	0.63	0.63	0.61
C reactive protein ≥ 19 mg/l	2.2 (1.4 to 3.5)	0.0005	0.60	0.62	0.62	0.58
Age ≥ 55 years	2.1 (1.4 to 3.3)	0.001	0.59	0.61	0.61	0.58
Male sex	1.6 (1.0 to 2.5)	0.044	0.38	0.72	0.59	0.52
Previous or current smoker	1.6 (1.0 to 2.5)	0.040	0.66	0.66	0.66	0.55
Disease duration ≥ 6 months	0.8 (0.5 to 1.2)	0.274	0.51	0.49	0.49	0.45
DRB1*04 present	1.3 (0.7 to 2.5)	0.371	0.58	0.48	0.48	0.59
DAS28 ≥ 5.1	1.2 (0.8 to 1.9)	0.307	0.55	0.55	0.55	0.51
Pain VAS ≥ 44 mm	1.0 (0.6 to 1.5)	0.951	0.53	0.52	0.52	0.47
HAQ score ≥ 0.9	1.0 (0.6 to 1.6)	0.976	0.53	0.51	0.51	0.49

Continuous variables are dichotomised by their median values and anti-CCP, RF, DRB1*04 as to whether they are present or absent. Radiological joint damage is defined as an end point Larsen score of ≥ 10 or more (the median value).

†Upper limit of expected number of false significances = 0.26.

CCP, cyclic citrullinated peptides; CI, confidence interval; DAS28, 28 joint disease activity score; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; RF, rheumatoid factor; VAS, visual analogue scale.

logistic regression model: Larsen score, anti-CCP, RF, ESR, C reactive protein, patient age, smoking status, and sex.

In the forward stepwise logistic regression analysis (table 4), baseline Larsen score, anti-CCP and ESR turned out to be the most important variables predicting *radiological joint damage*. The odds ratio (95% CI) for baseline Larsen score was 14.9 (8.0 to 27.6), for anti-CCP 4.7 (2.5 to 8.7), and for ESR 2.0 (1.1 to 3.5). The model allowed correct classification in 78% of cases (accuracy). The sensitivity, specificity, PPV, and NPV were 0.79, 0.77, 0.79, and 0.77, respectively. About 50% of the "variance" (Nagelkerke R^2) in radiological damage was explained by the model.

Baseline Larsen score, anti-CCP, and ESR similarly appeared to be the best predictors for *radiological progression* (table 5). The odds ratio (95% CI) for Larsen score was 9.3 (5.3 to 16.2), for anti-CCP 3.0 (1.7 to 5.2), and for ESR 1.8 (1.0 to 3.1). Correct classification was obtained in 75% of the patients. The sensitivity, specificity, PPV, and NPV were 0.75, 0.75, 0.77, and 0.73, respectively. The explained variance was somewhat lower, at about 40%.

Thirty six per cent of the patients with x rays available had a baseline Larsen score of zero, and possible predictors were looked for separately in this group of patients. A forward logistic regression analysis showed that anti-CCP was the best predictor of radiological progression (OR (95% CI), 3.7 (1.6 to 8.6), $p = 0.002$), in this case defined as a Larsen score above zero at two years.

DISCUSSION

Joint damage accounts for a considerable part of the disability caused by rheumatoid arthritis.¹⁷ Accordingly, preventing and diminishing joint damage is an important treatment goal in early rheumatoid arthritis. Hence, reliable predictors of joint damage are required.

This study of patient with rheumatoid arthritis in clinical practice, diagnosed within the first year of the disease and followed prospectively in a structured way, showed that the presence of anti-CCP is associated with joint destruction as measured by the Larsen score. Thus anti-CCP positive patients had significantly more joint damage than patients without this antibody, both at baseline and at the end of the study. Furthermore, prediction analyses showed that among several demographic and clinical variables anti-CCP came out as an important independent predictor, surpassed only by baseline x ray score.

Previous studies on the possible predictive value of antibodies to citrullinated proteins for x ray changes have provided various messages. In two studies by our group, an association between baseline antikeratin and antifilaggrin antibodies (AKA and AFA) and Larsen scores after two and five years of follow up in patients with early rheumatoid arthritis was described.^{18, 19} Similar findings of a higher risk for radiological progression in patients with AKA have been presented by Paimela *et al*,²⁰ Vasiliauskiene *et al*,²¹ and Meyer *et al*.²² Recently, Genevay *et al* reported in a study on a small

Table 3 Univariate analysis of baseline variables as possible predictors of radiographic progression

Variable	OR (95%CI)	P value†	Sensitivity	Specificity	PPV	NPV
Larsen score ≥ 4	9.9 (5.8 to 16.5)	0.0005	0.76	0.76	0.77	0.74
Anti-CCP present	2.9 (1.8 to 4.6)	0.0005	0.68	0.58	0.64	0.62
RF present	2.6 (1.6 to 4.1)	0.0005	0.72	0.50	0.61	0.62
ESR ≥ 29 mm/h	2.5 (1.6 to 4.0)	0.0005	0.62	0.61	0.63	0.59
C reactive protein ≥ 19 mg/l	1.9 (1.2 to 3.0)	0.006	0.57	0.59	0.63	0.59
Age ≥ 55 years	2.1 (1.3 to 3.3)	0.001	0.59	0.59	0.61	0.57
Male sex	1.8 (1.1 to 2.9)	0.017	0.38	0.72	0.62	0.52
Previous or current smoker	1.9 (1.2 to 3.0)	0.009	0.68	0.70	0.58	0.57
Disease duration ≥ 6 months	0.8 (0.5 to 1.3)	0.419	0.52	0.43	0.5	0.45
DRB1*04 present	1.2 (0.6 to 2.3)	0.544	0.58	0.46	0.51	0.54
DAS28 ≥ 5.1	1.2 (0.8 to 2.0)	0.324	0.55	0.51	0.55	0.50
Pain VAS ≥ 44 mm	0.9 (0.6 to 1.5)	0.811	0.53	0.46	0.52	0.46
HAQ score ≥ 0.9	1.0 (0.7 to 1.6)	0.843	0.53	0.48	0.53	0.46

Continuous variables are dichotomised by their median values and anti-CCP, RF, DRB1*04 as to whether they are present or absent. Radiological progression is defined as a difference in Larsen score between end point and baseline of ≥ 8 (the median difference).

†Upper limit of expected number of false significances = 0.26.

CCP, cyclic citrullinated peptides; CI, confidence interval; DAS28, 28 joint disease activity score; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; RF, rheumatoid factor; VAS, visual analogue scale.

Table 4 Independent predictors of radiological damage (stepwise logistic regression)

	β	SE	Wald	p Value	OR (95% CI)
Larsen baseline score*	2.701	0.315	73.2	0.0005	14.9 (8.0 to 27.6)
Anti-CCP†	1.542	0.320	23.2	0.0005	4.7 (2.5 to 8.7)
ESR‡	0.671	0.300	5.0	0.025	2.0 (1.1 to 3.5)
Constant	-2.528	0.345	53.7	0.0005	

*Variable entered on step 1.

†Variable entered on step 2.

‡Variable entered on step 3.

CI, confidence interval; OR, odds ratio; SE, standard error.

number of patients with rheumatoid arthritis that AKA and AFA, assessed in early disease, were associated with Larsen score after as long as eight years.²³ However, in a recent study by Meyer *et al*,²⁴ AKA did not predict radiological progression (assessed by the modified Sharp score).

Anti-CCP—that is, antibodies to synthetic cyclic peptides containing citrulline—have higher sensitivity for the diagnosis of rheumatoid arthritis and a very high specificity, making this antibody more useful than AKA, AFA, and APF, and even more so if it turns out to have predictive properties. That this may be the case has been shown by, among others, Visser *et al*,⁹ who developed a prediction model for erosive arthritis (modified Sharp score) in which anti-CCP was strongly associated with erosive arthritis (more than RF: odds ratio 4.58 v 2.99).

Most recently, Vencovsky *et al* studied the predictive value of autoantibodies in 64 patients with early rheumatoid arthritis.²⁵ In agreement with our data, anti-CCP positivity predicted progression of Larsen score over two years better than RF, and the presence of both antibodies did not increase the predictive ability.

Recently, Meyer *et al* reported the sensitivity, specificity, and positive and negative predictive value of anti-CCP in predicting radiological progression (modified Sharp score) after five years of observation.²⁴ Their results were very similar to the data reported here.

Our investigation confirms previous suggestions that anti-CCP may reflect the development of joint damage in rheumatoid arthritis and that the presence of anti-CCP is an important predictor of radiological outcome. However, one should be aware that anti-CCP shares a feature of all other available predictors—namely, that a substantial number of patients with the predictor still do not develop radiological damage in the near future.

Thus as no single variable can assure correct prediction in the individual case, combined scores have been sought. In the 1990s, van Zeben *et al*²⁶ and van der Heijde *et al*²⁷ have developed logistic regression models including various combinations of baseline features for predicting radiographic change, although not including anti-CCP. The accuracy of these models varies between 70% and 80%. In 2001, Combe *et al*²⁸ developed a composite index for predicting radiological damage including baseline x ray score (modified Sharp score), RF, DRB1*04, and pain (anti-CCP was not measured).

This model had a sensitivity of 0.78 and a specificity of 0.85 (stepwise logistic regression). In the present study the stepwise logistic regression analysis included baseline Larsen score, anti-CCP, and ESR. This combination provided similar sensitivity and specificity for radiological progression, at 0.79 and 0.77, respectively.

HLA-DRB1 typing was available in only 49% of our patients but, in contrast to the observation made in the study by Combe *et al*,²⁸ the presence of DRB1*04 was not found to be associated with radiological damage or progression. Other studies have also failed to confirm this association—for example, Rau *et al*²⁹ did not find any relation between erosive disease and shared epitopes in a long term study on patients with early rheumatoid arthritis. Similarly, Eberhardt *et al*³⁰ did not find the genotype to be strongly associated with disease severity after two and five years. In another study, by Matthey *et al*,³¹ a predictive value of shared epitopes for radiological changes was detected but it was restricted to RF negative patients. The reason for this discrepancy is not clear. Further studies on larger numbers of patients might solve this issue.

Kroot *et al*,⁸ in a study of patients with early rheumatoid arthritis, found that anti-CCP positive patients at follow up had developed significantly more radiological damage than patients without this antibody. However, in a multiple regression analysis the presence of RF was a better predictor of radiological change (modified Sharp score) after three years than the presence of anti-CCP. Conversely, anti-CCP but not RF was the best predictor in our regression models. Maybe this discrepancy reflects the fact that the study by Kroot *et al* employed the somewhat less sensitive CCP1 test. Anti-CCP and RF are strongly interrelated and their contribution to explaining and predicting joint damage may reflect clinically relevant disease processes.

As most data lend support to the impression that anti-CCP and RF overall have a similar ability to predict radiological outcome, the different performance in the two regression models might be explained by methodological differences in the assays used, or by different cut off values chosen for anti-CCP and RF.

As shown in the prediction models by, for instance, Combe *et al*²⁸ and Kroot *et al*,⁸ variables reflecting disease activity also contribute to the prediction of joint damage. In the present study ESR and C reactive protein, but not pain, DAS28, or

Table 5 Independent predictors of radiological progression (stepwise logistic regression)

	β	SE	Wald	p Value	OR (95% CI)
Larsen baseline score*	2.226	0.284	61.5	0.0005	9.3 (5.3 to 16.1)
Anti-CCP†	1.088	0.289	14.1	0.0005	3.0 (1.7 to 5.2)
ESR‡	0.567	0.282	4.0	0.045	1.8 (1.0 to 3.1)
Constant	-1.904	0.295	41.6	0.0005	

*Variable entered on step 1.

†Variable entered on step 2.

‡Variable entered on step 3.

CI, confidence interval; OR, odds ratio; SE, standard error.

HAQ, showed a significant association with radiological outcome, although only ESR was included in the regression models. Smoking is a known risk factor and is proposed to be a severity factor for rheumatoid arthritis.³² In this study previous or current smoking gave a significant odds ratio both for radiological damage and progression—possibly a further argument for using smoking as a severity factor in rheumatoid arthritis.

Most of the attempts to find a prediction model suitable for use in the individual patient have, as in the present study, resulted in an accuracy (the ability to classify the patients correctly) for radiological damage of around 70–80% and an explained variance of up to about 50%.² These figures may appear discouraging. However, in recent years new data on various factors with predictive ability have been identified, and combinations of these factors have been shown to increase predictability. In line with this, our study provides good evidence for an association of anti-CCP with radiological change and shows that this antibody is an independent predictor of radiological joint damage and progression. Though prediction in early rheumatoid arthritis still falls far short of perfection, the use of anti-CCP in clinical practice may contribute to increasing the ability of rheumatologists to make judicious treatment decisions.

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MEMBERS OF THE BARFOT STUDY GROUP

Monica Ahlmén, Johan Bratt, Kristina Forslind, Ingjald Hafström, Catharina Keller, Ido Leden, Bengt Lindell, Ingemar Petersson, Christopher Schaufelberger, Björn Svensson, Annika Teleman, Jan Theander

Authors' affiliations

K Forslind, B Svensson, Section of Rheumatology, Helsingborgs lasarett, Helsingborg, Sweden

M Ahlmén, Rheumatology Department, Sahlgrenska University Hospital, Mölndal, Sweden

K Eberhardt, Rheumatology Department, University Hospital, Lund, Sweden

I Hafström, Rheumatology Department, Karolinska Institutet at Huddinge University Hospital, Stockholm, Sweden

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